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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,790	03/22/2001	Keith D. Allen	R-855	5557

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,790	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43,49,50 and 52-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43,49,50 and 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 40-43, 49, 50 and 52-57 are pending in the specification.

This Office Action is in response to the Amendment filed on 2/11/05.

Response to Amendment

Claims 40-43, 49, 50 and newly added claims 52-57 stand under 35 U.S.C.102/112 1st paragraph is maintained for reasons set forth of the record mailed on 11/15/04 and further discussed below.

Claims 40-43, 49, 50 and newly added claims 52-57 are rejected under 35 U.S.C. 112 1st (written description) for reasons discussed below.

Claim 40 is rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Response to Arguments

Claims 40-43, 49, 50 and newly added claims 52-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

Newly added claims 52-57 are rejected for lack of utility for same reasons as applied to claims 40-44, 46-50 as discussed in the office action mailed on 11/15/04. The following is answers to Applicant's argument regarding this rejection.

In response to this rejection, Applicant asserts that the claims are drawn to a transgenic mouse having a disrupted sulfotransferase gene and a transgenic mouse whose genome comprises a null allele which comprises exogenous DNA. Applicant argues that the claimed invention has patentable utility according to utility guidelines set forth in MPEP because the claimed invention has a well-established utility. Applicant assert that the skilled in the art would

immediately appreciate how to use a knockout mouse because any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted gene regardless of specific phenotypes, characterizations or properties of the knockout mouse. Applicant further cites a passage at NIH website which indicate that knockout mice represent a critical tool in studying gene function. Furthermore, Applicant asserts that the newly amended claims drawn to transgenic mouse comprising null-reporter alleles "is an indispensable starting point for studying the function of every gene"(Austin et al., 2004), "is an invaluable tool for investigating gene function on a genomic scale"(Molecular biology of Cell, Albert, 4th ed., Garland Science (2002), "is a powerful tool to investigate directly the importance and function of the gene" (Genes VII, Oxford university 2000), "offers a powerful approach to study gene function in a mammalian organism," (Joyner, Gene targeting: A Practical Approach, Oxford University Press 2000), "has revolutionized our ability to study gene function in cell culture *in vivo*," (Matise, Production of Targeted Embryonic Stem Cell Clones), and "provide an important means for understanding gene function."(Crawley, what's wrong with my mouse behavioral phenotype of transgenic and knockout mice, Wiley-Liss 2000). Moreover, Applicant asserts that the knockout mouse have a clear, specific and unquestionable utility as with gas chromatographs, screening assays and nucleotide sequence techniques as taught by MPEP 2107.01,I. Furthermore, Applicant also asserts that the claimed invention is useful for a particular purpose since the mouse has specific disclosed phenotype. Applicant argues that the utility of the claimed inventions does not depend on a correlation between the disclosed phenotype and a disease in human according to *In re Brana*, in which the court decided that the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a 112 1st

rejection because the PTO had not satisfy the initial burden of providing evidence to doubt the asserted utility. Applicant asserts that similar to *Brana*, Applicant has asserted that the claimed invention is useful for a particular purpose, and such assertion would be considered credible by a person of ordinary skill in the art. Applicant argues that since the claimed knockout mouse has specific phenotypes, it is recognized in the art as a widely accepted model for determine gene function, both in mouse and humans (Austin and Doetschman). Applicant asserts that the Federal court found that utility had been demonstrated because the claimed compound had activity against a murine tumor implanted in a mouse in *Brana*, which is similar to the instant case in which the knockout mouse with a specific gene disrupted is a widely accepted model. Applicant argues that definitive proof that the phenotype observed in the null mouse would be the same as those in human is not a prerequisite to satisfying the utility requirement. Furthermore, Applicant argues that the present invention requires no further research to establish any utility because the specification has disclosed the sulfotransferase gene is associated with a condition, such as anxiety, which has immediate benefit to the public. Moreover, Applicant asserts that the claimed mouse has specific utility because the use of sulfotransferase gene with any of the condition related to the liver, salivary glands and behavior is specific to this mouse even if there were many other genes associated with these conditions. Applicant asserts that use of the mouse to study gene function is credible and specific. Applicant argues that the examiner has not set forth any reason to doubt the objective truth of the statements made in the specification, particularly with respect to the claimed transgenic mouse. Applicant thus concludes that the claimed invention has credible, substantial and specific utility which satisfies the statue of 35 U.S.C. 101.

These arguments have been fully considered but deemed unpersuasive. The reasons for the utility and non-enablement rejection were discussed in detail in the office action mailed on 11/15/04 and in the utility rejection discussed above. In response to Applicant's response regarding any knockout mouse has a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible." In the instant case, the utility that applies to any knockout mouse is not specific to the claimed invention, the sulfotransferase transgenic mouse having a null allele that comprises exogenous DNA. It was well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility, of which must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art as indicated by the quotations cited by Applicant, for example, studying gene function. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial. The utility guidelines specifically state that further research is not a "substantial utility." The MPEP states "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define

"substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved..." In the instant case, further study of mice would have been required to determine how to use the mouse of applicant's invention according to the embodiments described in the specification since the overall phenotype of the claimed mice does not correlate with any disorder; Therefore, further study would be required to determine how to use the mice to study a disorder, screening drugs and treatment for such disorder (the asserted utility in the specification). With regard to the well-established utility of studying gene function as asserted by Applicant, Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). As such, a knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using the claimed mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that this case law applies to the instant case. In the *Brana* decision, the court

concluded that the mouse tumor models (leukemia cell lines were originally derived from lymphocytic leukemia in mice) represent a specific disease against which the claimed compounds were alleged to be effective. As such, the claimed compound has credible, substantial and specific utility. In *Brana*, the asserted utility meets the requirement of the statue because the claimed compounds are effective in a valid and specific mouse tumor model. However, in the instance case, the claimed knockout mouse does not have a credible, substantial and specific use because the specification does not teach what specific disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. Although Applicant asserts that the claimed mouse is a widely accepted model, the prior art is in fact silent on the claimed mouse thus does not recognize any well-established utility for the claimed mouse. The examiner is not asking for definitive proof that the phenotype of the null mouse is same as those in human, but some credible teaching from the specification about what type of model the claimed mouse represents. Moreover, the utility of using the claimed mouse to study sulfotransferase function or association to the phenotype is not a credible, substantial and specific utility for reasons discussed above. Applicant's argument that the claimed mouse is a model for studying anxiety is not credible because the claimed phenotypes are decreased anxiety and aggressive behavior, thus it is unclear whether said gene is involved in decrease anxiety or increase anxiety. Moreover, the newly added claims recite phenotype such as liver abnormality (patchy pallor of acinar zone 3, eosinophilic globules with intranuclear invaginations etc.), salivary gland and Harderian gland abnormality. It is unclear how these phenotypes are related to anxiety. For

reasons discussed in the previous office actions and above, it is unclear whether all the phenotypes recited are result directly from the disruption of the sulfotransferase, secondary to said disruption or compensatory effect from other genes. Clearly, further research is required to determine the function of the sulfotransferase gene, thus said mouse lack substantial utility. Therefore, unlike *Brana,* the instant specification fails to provide a credible, substantial and specific utility for the claimed mouse.

For reasons given in the previous office action and above, the specification fails to disclose a credible, substantial and specific use for the claimed mouse and one skilled in the art would not know how to use the claimed mouse according to the embodiments disclosed by the instant specification. This rejection is thus maintained. This rejection is also applied to the newly presented claims 52-57 for same reasons as discussed in the previous office action and above.

Claim Rejections - 35 USC § 112

Claims 40-43, 49, 50 and newly added claims 52-57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Newly added claims 52-57 are rejected for lack of enablement for same reasons as discussed in the office action mailed on 11/15/04. The following is answers to Applicant's argument regarding this rejection.

In response to this rejection, Applicant argues that the claimed mouse has patentable utility for reasons discussed above. Applicant further asserts that the amended claims are drawn

to a mouse having a null sulfotransferase allele, which includes a mouse having a single null allele and a mouse having two null alleles. Applicant asserts that the specification clearly set forth how to make and use the mice, wherein the heterozygous mice are useful for breeding homozygous mice, gene expression analysis, phenotype evaluation, and the homozygous mice are useful to determine the function of the gene. Applicant asserts that any phenotype associated with the heterozygous and homozygous null mice are inherent to the mice, wherein many of the phenotype will not be associated with genotype are wild type phenotypes. Moreover, Applicant argues that the control mice and the claimed mice have same background. Lastly, Applicant asserts that the instant claims do not recite a phenotype for the heterozygous mice, rendering the examiner's comments with regard the phenotype confusing. Applicant thus concludes that the claimed mouse is enabled by the instant specification.

These arguments have been fully considered but deemed unpersuasive. The reasons for non-enablement of the invention are discussed in detail in the office action mailed on 11/15/04. The claimed mouse has no patentable utility for reasons discussed above. The enablement requirement requires the specification not only teaching how to make but also how to use the claimed invention. Although the specification teaches how to make the claimed mouse, it fails to teach how to use the mouse according to the embodiment disclosed in the specification. Using the homozygous mouse to study sulfotransferase gene function is not a credible, substantial and specific utility for reasons discussed above. Since the homozygous mouse does not have a patentable utility, the heterozygous mouse used to breed homozygous mouse does not have patentable utility either. Using the heterozygous mouse for phenotype analysis is not a credible, substantial and specific utility because the heterozygous mouse does not exhibit any phenotype

as disclosed in the specification. Thus, it is unclear how to use it in the analysis of phenotype evaluation. In addition, use of the heterozygous mouse for studying a gene expression of which the function is unknown is not a substantial utility. Since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Regarding Applicant's argument of the inherency of the phenotype to the claimed mouse including wild type phenotype, the examiner does not understand what is so called "wild type phenotype" which is not described in the specification, and what is the relevance of such "phenotype" to the enablement of the claimed mouse.

Regarding Applicant's argument of control mouse has the same background as the claimed mouse, Applicant is reminded the unpredictability of the phenotype of the transgenic mouse is based on the background of the transgenic mouse itself, not the control mouse. Although Applicant uses gender, age and strain matched wild type controls, the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background gene, and other unknown mutations in the genetic background (see pages 107 last paragraph through page 108 1st paragraph of Crawley, also action mailed on 11/15/04, page 7-8 bridging paragraph). Lastly, the amended claim does not recite a phenotype for the heterozygous mouse, the examiner's argument with respect to heterozygous mouse in the previous office action is moot. However, Applicant is reminded that a transgenic mouse having no phenotype is not enabled because one skilled in the art would not know how to use the claimed mouse with no phenotype (see action mailed on 11/15/04, page 6, 2nd paragraph, lines 4-6, and page 7-8

bridging paragraph for reasons). Therefore, for reasons discussed in the previous office action and above, the claimed mouse and the method for making said mouse are not enabled by the instant specification.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-40, 49, 20, 52-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the

claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite a transgenic mouse whose genome comprises a null endogenous sulfotransferase allele. There are a large number of endogenous sulfotransferases known at the time of filing, including human liver DHEA, TS PST and TL PST. However, the specification only discloses a transgenic mouse comprises a null endogenous sulfotransferase encoded by SEQ ID NO:19 that has the recited phenotype. The specification fails to describe any transgenic mouse having a null allele of any other sulfotransferase that has the same phenotype. Since the art teaches that the phenotype of the transgenic mouse is unpredictable, the specification would have to describe the complete structure (both genotype and phenotype) of the claimed genus of transgenic mouse to satisfy the written description requirement. However, the specification fails to describe the genotype and phenotype of the claimed transgenic mice except the one with null sulfotransferase encoded by SEQ ID NO:19. As such, the specification fails to describe the claimed genus with a representative number of species by their completes structure or other identifying characteristics. Therefore, the written description requirement is not met.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "pseudopregnant mouse gives birth to a chimeric mouse" renders the claim indefinite because is unclear how a "pseudopregnant mouse" can give birth.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
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